34 The Influence of Antiphospholipid Antibodies on the Protein C Pathway

Philip G. de Groot and Ronald H. W. M. Derksen

Introduction

Blood coagulation is the mechanism that maintains the integrity of the high pressure closed circulatory system of blood. To prevent extravasations of the blood after injury, the hemostatic mechanism, which includes platelets, coagulation, and fibrinolytic proteins in plasma and endothelial cells, is activated. A platelet plug will be formed that prevents further blood loss. Subsequently, the coagulation cascade replaces the unstable platelet plug by the stable fibrin clot. An essential feature of the hemostatic reaction is that platelet deposition and fibrin formation is localized and limited to the immediate area of the injury. Therefore, it is essential that different natural anticoagulant mechanisms are operative to regulate coagulation. When the natural anticoagulant mechanisms do not function optimally, this will lead to thrombotic complications. One of the most important natural anticoagulant systems is the protein C pathway [1, 2]. The high number of patients that have been described with heterozygous protein C or protein S deficiency and familial thrombophilia highlight the clinical importance of the anticoagulant properties of protein C and protein S. Complete protein C deficiency represents a potentially lethal condition. Thrombotic complications can be controlled with protein C replacement therapy [3, 4].

Antiphospholipid antibodies (aPL) are a heterogeneous group of autoantibodies defined by 2 very distinct assay methods. One group, called lupus anticoagulant (LA), is defined as antibodies that inhibit in vitro phospholipid dependent coagulation assays. The second group, anticardiolipin antibodies (aCL), is defined by their ability to bind to negatively charged phospholipids in an enzyme-linked immunosorbent assay (ELISA) [5]. Paradoxically, the presence of aPL in plasma is a major risk factor for the development of arterial and venous thrombosis and is not associated with a bleeding diathesis, as would be expected when clotting times are prolonged [6].

The pathophysiology that underlies the relation between the aPL in plasma and the risk for thrombo-embolic complications is still unexplained [7] but an attractive hypothesis is that the aPL interfere with (one of) the natural anticoagulant pathways in the body. In this chapter we will discuss one of these possibilities: a link between aPL and the protein C system.

Protein C axis

In the early 1980s, a phospholipid dependent antithrombotic pathway was described that soon turned out to be one of the body's major defense mechanisms to uncontrolled coagulation. Vascular endothelium expresses a membrane bound receptor on its surface, thrombomodulin, which binds thrombin and thereby alters its substrate specificity. Thrombin bound to thrombomodulin is no longer able to activate platelets or to convert fibrinogen into fibrin, but it converts a vitamin K dependent protein, protein C, into activated protein C (APC) [8]. APC is a physiological anticoagulant via its potential to inactivate clotting factors Va and VIIIa, which results in inhibition of further thrombin formation (Fig. 34.1). Protein C activation by thrombin–thrombomodulin complex is further enhanced about 20-fold when protein C is bound to the endothelial cell protein C receptor (EPCR). Thrombomodulin also influences fibrinolysis. Thrombin bound to thrombomodulin activates TAFI (thrombin inducible fibrinolysis inhibitor, carboxypeptidase B). TAFI removes carboxyterminal lysine residues from fibrin, thereby preventing the binding of tissue plasminogen activator (tPA) and plasmin(ogen) to fibrin. TAFI thus reduces fibrinolysis. Activation of TAFI is thought essential for the stability of a fibrin clot [9].

The role of the protein C axis extends beyond hemostasis. Activated protein C has potent anti-inflammatory properties and administration of human activated protein C significantly decreases mortality in patients with severe sepsis [10]. Furthermore protein C has a role in cell survival and cell proliferation [11].

Protein C is a vitamin K dependent glycoprotein with a molecular weight of 62 kDa. In blood it circulates as an inactive zymogen, mostly in the form of a two chain molecule [12]. The thrombin–thrombomodulin complex activates protein C by

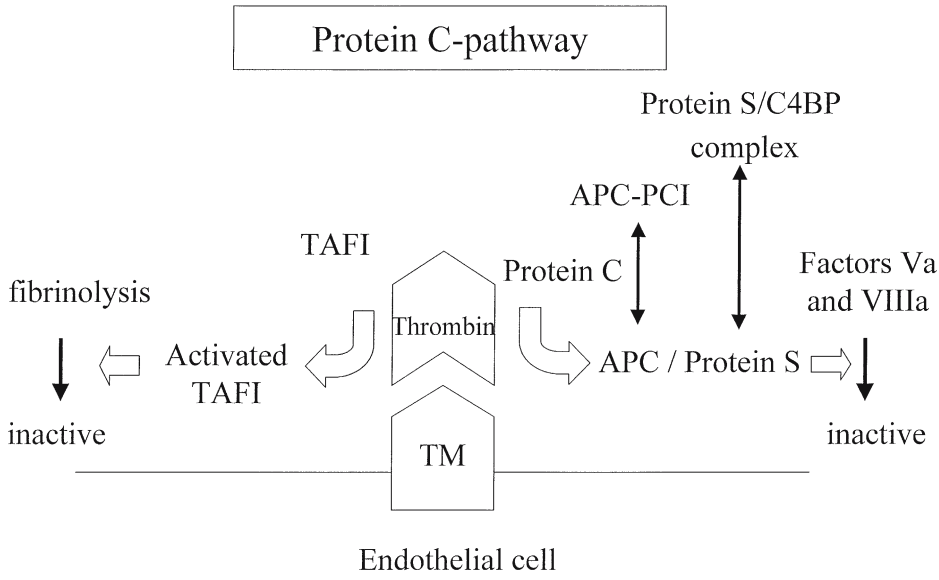

Figure 34.1. The protein C pathway.